PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32761A/UNZ	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/13960	International filing date *(day/month/year)* 09.12.2003	Priority date *(day/month/year)* 10.12.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/00		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.06.2004	10.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13960

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Sequence listings part of the description, Pages

41-116 as originally filed

Claims, Numbers

1-18 as originally filed

Drawings, Sheets

1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 18

   because:

   ☒ the said international application, or the said claims Nos. 18 (method of treatment) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9-18
	No:	Claims	1-8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	18

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35 (2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: MERKLER D ET AL: "Locomotor recovery in spinal cord-injured rats treated with an antibody neutralizing the myelin-associated neurite growth inhibitor Nogo-A" JOURNAL OF NEUROSCIENCE, vol. 21, no. 10, 15 May 2001, pages 3665-3673, XP002293416 ISSN: 0270-6474

D2: POT C ET AL: "Nogo-A expressed in Schwann cells impairs axonal regeneration after peripheral nerve injury" JOURNAL OF CELL BIOLOGY, vol. 159, no. 1, 14 October 2002, pages 29-35, XP002293417 ISSN: 0021-9525

D3: RAINETEAU O ET AL: "Improved locomotor recovery in spinal cord injured rats treated with the monoclonal antibody IN-1" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 2, 2001, page 1833, XP001199820

D4: LI W ET AL: "NEUTRALIZATION OF MYELIN - ASSOCIATED NOGO - A BY A NOGO RECEPTOR - Fc FUSION PROTEIN." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2002, 2002, pages Abstract No. 333.2 URL-http://sf, XP001199824 & 32ND ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; ORLANDO, FLORIDA, USA; NOVEMBER 02-07, 2002

D5: PAPADOPOULOS C ET AL: "Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat" ANNALS OF NEUROLOGY, vol. 51, no. 4, April 2002, pages 433-441, XP008034394 ISSN: 0364-5134

D1 and D3 disclose the treatment of adult rats having a dorsal overhemisection of the spinal cord with the monoclonal antibody (mAb) IN-1 raised against Nogo-A. Treatment with the antibody improved the functional recovery which results from a meaningful rewiring of the motor systems (see the abstracts). Results are consistent with earlier findings showing that IN-1 treatment after injuries of the adult CNS leads to functional benefits (D1, p.3670, left-hand column, 2nd §) and that the mAb IN-1 allows sprouting and reorganization of lesioned as well as unlesioned fibers in adult rats at a degree that is normally only observed after perinatal lesions (D1, p.3671, left-hand oclumn, last §).

D2 discloses the generation of transgenic mice expressing the rat Nogo-A gene in order to investigate in vivo the inhibitory characteristics of Nogo-A (p.29, left-hand column, 1st §). Postnatal expression of Nogo-A in Schwann cells results in a significant delay in axon regeneration in the denervated adult mouse sciatic nerve (p.33, left-hand column, last two lines - right-hand column, first lines). The inhibitory property of Nogo-A is demonstrated by enhanced regeneration and functional recovery of lesioned CNS tracts resulting from in vivo application of the mAb IN-1. Blockade of Nogo-A signaling by antibody is proposed for therapies of CNS injuries including spinal cord or brain trauma and stroke (p.33, right-hand column, 3rd §).

D4 discloses a recombinant Nogo receptor-Fc fusion protein which inhibits Nogo66 binding to the Nogo receptor and reverses the inhibitory effects of Nogo-A-containing CNS myelin thus disrupting the NogoA-NogoR interaction and promoting neurite growth in the presence of CNS myelin (abstract).

D5 discloses that following ischemic stroke and treatment with IN-1 adult rats demonstrated functional recovery (see the abstract).

NOVELTY & CLARITY

Because neither the feature "with a dissociation constant <1000nM" itself nor the proteins defined by this term are clear, the wordings of claim 1 have been interpreted as "a binding molecule which is capable of binding to the human NogoA or human NiG or human NiG-D20

or NogoA_623-640". As a consequence it is considered that any antibody anti NogoA or any soluble Nogo receptor is anticipating the novelty of claim 1. Moreover in claims 2 & 3 a binding molecule is defined as comprising at least one antigen binding site being at least 50% homologous to given sequences (SEQ ID NO: 8-13). This wording does not allow a clear definition of a binding molecule. Claims 4-6 are also not clear because of the definition of a binding molecule only with sequences of CDR and because of the terms "direct equivalent thereof". As a consequence claim 1 is neither novel over the mAb IN-1 disclosed in documents D1, D2, D3 and D5 nor over the Nogo receptor-Fc fusion protein disclosed in D4 and claims 2-8 are not considered novel over the IN-1 antibody disclosed in D1, D2, D3 and D5. Claims 15-18 are not novel as far as they relate to any of claims 1-8.

Claim 9 relating to a binding molecule comprising SEQ ID NO: 2 & 3 and dependant claims 10-14 are novel over the mAb IN-1. The use and pharmaceutical composition claims 15-18 are novel as far as they relate to claim 9.

INVENTIVE STEP

Claim 9 is novel over the mAb IN-1 disclosed in D1 but this claim is not considered to involve an inventive step for the following reasons. Document D1 discloses the antibody IN-1 binding to the Nogo-A and its use in a treatment which improved the functional recovery of adult rats having a dorsal overhemisection of the spinal cord (see above).

Claim 9 is considered to relate to the mouse anti Nogo-A antibody 11C7 disclosed in the present application since SEQ ID NO:2 is the variable part of the heavy chain of 11C7 with leader sequence and SEQ ID NO:3 is the light chain of 11C7 with leader sequence. The antibody 11C7 differs from the IN-1 antibody by the fact it is a different antibody. The problem to be solved by the present invention may therefore be regarded as the provision of an alternative anti Nogo-A antibody. The solution appears to solve the problem posed but is not considered to involve an inventive step since it is a matter of routine to prepare antibodies and the positive properties of IN-1 as shown in D1 represent an incentive for the skilled person to develop other anti NogoA antibodies.

11C7 does not appear to have any particular property that would support the inventive step

of claim 9. That 11C7 binds NogoA and also identifies human NiG, cynomolgus NiG cell lysate and rat NiG-D20 in western blot (see description, p.31) is not rendering 11C7 inventive over IN-1 since whether IN-1 identifies these proteins or not is not known. Moreover in the light of the examples it is not clear whether the feature "with a dissociation constant <1000nM" is supported by the description (example 7). Without clear experiment supporting that the antibody 11C7 has a particular and unexpected property no inventive step will be acknowledged to the antibody 11C7 of the present invention.

Because the antibody 11C7 is not considered as involving an inventive step the claims 10-14 and 15-18 as far as they relate to claim 9 are also not involving an inventive step.

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 15, 16 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.